Prospective isolation of hESC-derived hematopoietic and cardiomyocyte stem cells

Grant Award Details

Prospective isolation of hESC-derived hematopoietic and cardiomyocyte stem cells

Grant Type: Comprehensive Grant

Grant Number: RC1-00354

Investigator:

Name:	Irving Weissman
Institution:	Stanford University
Type:	PI

Disease Focus: Blood Disorders, Heart Disease, Immune Disease

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $2,471,386

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Grant Application Details

Application Title: Prospective isolation of hESC-derived hematopoietic and cardiomyocyte stem cells

Public Abstract: The capacity of human embryonic stem cells (hESCs) to perpetuate themselves indefinitely in culture and to differentiate to all cell types of the body has lead to numerous studies that aim to isolate therapeutically relevant cells for the benefit of patients, and also to study how genetic diseases develop. However, hESCs can cause tumors called teratomas when placed in the body and therefore, we need to separate potentially beneficial cells from hazardous hESCs. Thus, potential therapeutics cannot advance until the development of methodologies that eliminate undifferentiated cells and enrich tissue stem cells. In our proposal we hope to define the cell surface markers that are differentially expressed by committed hESC-derived stem cells and others that are expressed by teratogenic hESCs. To do this we will carry out a large screen of cell subsets that form during differentiation using a collection of unique reagents called monoclonal antibodies, many already obtained or made by us, to define the cell-surface markers that are expressed by teratogenic cells and others that detect valuable tissue stem cells. This collection, after filing for IP protection, would be available for CIRM investigators in California. We were the first to isolate mouse and human adult blood-forming stem cells, human brain stem cells, and mouse muscle stem cells, all by antibody mediated cell-sorting approaches. Antibody mediated identification of cell subsets that arise during early hESC differentiation will allow separation and characterization of defined subpopulations; we would isolate cells that are committed to the earliest lineage known to form multiple cell types in the body including bone, blood, heart and muscle. These cells would be induced to differentiate further to the blood forming and heart muscle forming lineages. Enriched, and eventually purified hESC-derived blood-forming stem cells and heart muscle stem cells will be tested for their potential capacity to engraft and improve function in animal models. Blood stem cells will be transplanted into immunodeficient mice to test their capacity to give rise to all blood cell types; and heart muscle stem cells will be transferred to mouse hearts that had an artificial coronary artery blockage, a model for heart attack damage. Finally, we will test the capacity of blood stem cell transplantation to induce transplantation tolerance towards heart muscle stem cells from the same donor cell line. Transplantation tolerance in this case means that the heart cells would be accepted as 'self' by the mouse that had it's unrelated donor immune system replaced wholly or in part by blood forming stem cells from the same hESC line that gave rise to the transplantable heart stem cells, and therefore would not be rejected by it's own immune system. This procedure would allow transplantation of beneficial tissues such as heart, insulin-producing cells, etc., without the use of immunosuppressive drugs.

Statement of Benefit to California:	The principle objective of this proposal is to develop reagents which, in combinations, can identify and isolate tissue-regenerating stem cells derived from hESC lines. The undifferentiated hESCs are dangerous for transplantation into humans, as they cause tumors. We propose to prepare reagents that identify and can be used to delete or prospectively isolate these tumor-causing undifferentiated hESCs. HESC-derived tissue stem cells have the potential to regenerate damaged tissues and organs, and don't cause tumors. We propose to develop reagents that can be used to identify and prospectively isolate pure human blood-forming stem cells derived from hESCs, and separately other reagents that can be used to identify and prospectively isolate pure heart-forming stem or progenitor cells. These "decontaminated" hESC-derived tissue stem cells may eventually be used to treat human tissue degenerative diseases. These reagents could also be used to isolate the same cells from somatic cell nuclear transfer (SCNT)-derived pluripotent stem cell lines from patients with genetic diseases. This procedure would enable us to analyze the effects of the genetic abnormalities on blood stem and progenitor cells in patients with genetic blood and immune system disorders, and on heart stem and progenitor cells in patients with heart disorders. The antibodies and stem cells (hESCs, tissue regenerating, etc) that will be isolated from patients with specific diseases will be invaluable tools that can be used to create model(s) for understanding the diseases and their progression. In addition, the antibodies and the stem cells generated in these studies are entities that could be patented or protected by copyright, forming an intellectual property portfolio shared by the state and the state institutions wherein the research was carried out. The funds generated from the licensing of these technologies will help pay back the state, will help support increasing faculty and staff (many of whom bring in other, out of state funds for their research), and could be used to ameliorate the costs of clinical trials. Only California businesses are likely to be able to license these antibodies and cells, to develop them into diagnostic and therapeutic entities; such businesses are the heart of the CIRM strategy to enhance the California economy. Most importantly, however, is that this research will lead to tissue stem cell therapies. Such therapies will address chronic diseases that cause considerable disability and misery, currently have no cure, and therefore lead to huge medical expenses. Because tissue stem cells renew themselves for life, stem cell therapies are one-time therapies with curative intent. We expect that California hospitals and health care entities will be first in line for trials and therapies, and for CIRM to negotiate discounts on such therapies for California taxpayers, thus California will benefit both economically and with advanced novel medical care.